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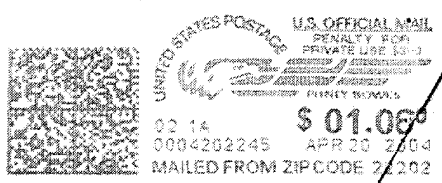


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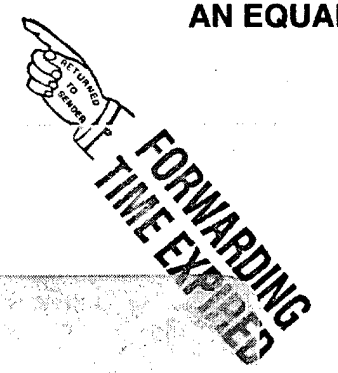


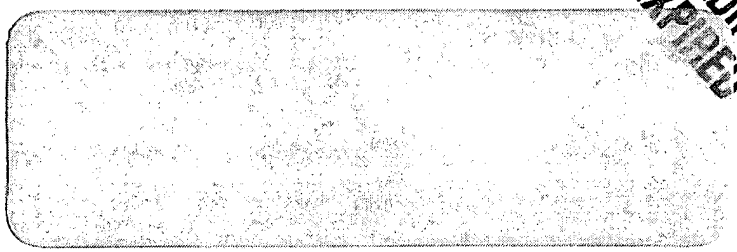

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/895,840 | 06/28/2001 | Catherine Guenther | R-409 | 4993 |

7590 04/20/2004

DELTAGEN, INC.
1003 Hamilton Avenue
Menlo Park, CA 94025

| EXAMINER | |
|---|---|
| QIAN, CELINE X | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1636 | |

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/895,840 | GUENTHER, CATHERINE | |
| | Examiner | Art Unit | |
| | Celine X Qian | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *97-127* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *97-127* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Claims 97-127 are pending in the application.

This Office action is in response to the Amendment filed on 1/16/04.

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/16/04 has been entered.

### *Response to Amendment*

The rejection to claims 59-61, 90-94 under 35 U.S.C.112 1st paragraph (written description) is moot in light of Applicant's cancellation of the claims.

The rejection of claims 50-58, 62-89, 95 and 96 under 35 U.S.C.112 1st paragraph (scope of enablement) is moot in light of Applicant's cancellation of the claims.

The rejection of claims 54-56, 57, 59-87 and 90-96 under 35 U.S.C. 112 2nd paragraph is moot in light of Applicant's cancellation of the claims.

The rejection of claims 50-58 under 35 U.S.C. 103 (a) is moot in light of Applicant's cancellation of the claims.

Claims 97-124 and 127 are rejected under 35 U.S.C. 112 1st paragraph for reasons discussed below.

Claims 123 and 124 are rejected under 35 U.S.C.112 2nd paragraph for reasons discussed below.

Claims 125 and 126 are rejected under 35 U.S.C. 103 (a) for reasons discussed below.

***New Grounds of Rejection***

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 97-124 and 127 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse comprising a disruption in an endogenous RORγ gene, wherein where the disruption is homozygous, the transgenic mouse lacks production of functional RORγ protein and exhibits a spleen abnormality, an abnormality of the thymus, an abnormality in the lymphocytes, an abnormality of lymph nodes, or an abnormality in the bone marrow, does not reasonably provide enablement for a transgenic mouse comprising a disruption in an endogenous RORγ gene, wherein where the disruption is homozygous, the transgenic mouse lacks production of functional RORγ protein and exhibits phenotypes of a kidney abnormality, a liver abnormality, or an abnormality in the bones. The specification also fails to provide enablement for a cell or tissue isolated from a heterozygous knockout mouse. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement

and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the Invention:

Claims 97-124 and 127 are drawn a transgenic mouse comprising a disruption in a RORγ gene, wherein the disruption is homozygous, the mouse does not produce functional RORγ protein, and exhibits phenotype for a spleen abnormality, an abnormality of the thymus, an abnormality in the lymph nodes, an abnormality in the lymphocytes, an abnormality in the bone marrow, a kidney abnormality, a liver abnormality, or an abnormality in the bones. The claims are further drawn to a cell isolated from said transgenic animal, and a method of producing said transgenic mouse.

Breadth of Claims:

In the instant case, claims 97-124 and 127 encompass a transgenic mouse that exhibits at least one of the phenotype such as a spleen abnormality, an abnormality of the thymus, an abnormality in the lymphocytes, a kidney abnormality, a liver abnormality, an abnormality in the lymph nodes, an abnormality in the bones, or an abnormality in the bone marrow, relative to a wild-type mouse. The specification does not provide an enabling disclosure for the full scope of the transgenic mouse as claimed. The only embodiment enabled by the specification within the scope of claims 97-124 and 127 is a transgenic mouse whose genome comprises a disruption in

an endogenous RORγ gene, wherein the disruption is homozygous, said mouse lacks production of the RORγ protein, and said mouse exhibits phenotypic feature of a spleen abnormality, an abnormality of the thymus, an abnormality of lymph nodes, an abnormality of bone marrow, or an abnormality in the lymphocytes, as compared to a wild type mouse, a method of producing such a transgenic mouse by homologous recombination in mouse ES cell, and a cell isolated from said homozygous knockout mouse. Thus, the breadth of the claims is broader than what is enabled by the instant specification.

Amount of guidance in the specification and Working Examples:

The specification discloses a RORγ transgenic knockout mouse, wherein the homozygous knockout mouse exhibits phenotype of a spleen abnormality, an abnormality of the thymus, an abnormality in the lymph nodes, an abnormality in the lymphocytes, and an abnormality in the bone marrow, a kidney abnormality, a liver abnormality, or an abnormality in the bones as compared to wild type mice. The specification does not provide specific teaching on how to use these mice with the disclosed phenotype. The specification prophetically teaches that the transgenic mouse can be used to screen drugs or as models for diseases, or screening agents that modulates a phenotype of said mouse. However, the specification fails to teach what type of diseases are the disclosed phenotypes related to, other than phenotypes that are consistent with lymphoma. The specification also fails to teach how to use the agent that modulates the phenotype associated with RORγ gene disruption. As such, one skilled in the art would not know how to use the transgenic mouse with phenotype of a kidney abnormality, a liver abnormality, or an abnormality in the bones, as a disease model or screen drugs for a specific disease. Moreover, the specification fails to teach how to use a cell isolated from the

heterozygous transgenic mouse. One skilled in the art would not know how to use such cell because heterozygous mouse does not have any phenotype, thus the cell isolated from said mouse would not have any phenotype either. Therefore, the teaching of the specification is limited.

The state of art and the predictability in the art

The state of art at the time of the filing is silent on a transgenic mouse whose genome comprises a disruption in an endogenous RORγ gene, wherein the disruption is homozygous, said mouse lacks production of the RORγ protein, and said mouse exhibits phenotypic feature of a spleen abnormality, an abnormality of the thymus, an abnormality in the lymph nodes, an abnormality in the lymphocytes, and an abnormality in the bone marrow, a kidney abnormality, a liver abnormality, or an abnormality in the bone marrow, as compared to a wild type mouse. The art does not provide any teaching regarding the relationship between RORγ function and a kidney abnormality, a liver abnormality, or an abnormality in the bones. The art is also silent on what type of disease is related to RORγ dysfunction that results in the disclosed phenotype. As such, whether transgenic mouse exhibits phenotype other than a spleen abnormality, an abnormality of the thymus, an abnormality in the lymphocytes, an abnormality with lymph nodes or an abnormality with bone marrow, which is consistent with lymphoma, can be used for a disease model or screening for drugs is unpredictable. One skilled in the art would have to engage in undue experimentation to use the invention as claimed. Therefore, the only enabled embodiment is a transgenic mouse whose genome comprises a disruption in an endogenous RORγ gene, wherein the disruption is homozygous, said mouse lacks production of the RORγ protein, and said mouse exhibits phenotypic features that are consistent with lymphoma,

including a spleen abnormality, an abnormality of the thymus, an abnormality in the lymphocytes, as compared to a wild type mouse, a method of producing such a transgenic mouse by homologous recombination in mouse ES cell, and a cell isolated from said homozygous knockout mouse.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 123 and 124 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 123 and 124 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: selecting embryonic stem cell that undergoes homologous recombination and comprises RORγ gene disruption.

The recitation of "wherein the pseudopregnant mouse gives birth" also renders the claims indefinite because a pseudopregnant mouse cannot give birth.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 125 and 126 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mansour et al (1988, Nature, vol. 336, No. 24, 348-352), in view of Medvedev et al. (Genomics 1997, Vol 46, pages 93-102, AG).

The claims are drawn to a RORγ gene-targeting construct and a murine embryonic stem cell comprising a disruption in an endogenous RORγ gene produced by using said construct. The recitation of "when introduced into a murine embryonic stem cell...a phenotypic abnormality..." implies the intended use of the claimed target construct, which carries no patentable weight because it does not change the structure of the targeting construct.

Mansour et al. teach a strategy for targeted disruption of the hprt gene and proto-oncogene int-2 in mouse embryonic stem cells and subsequent generation of knockout mice. Their teaching addresses the previous technical difficulty of obtaining embryonic stem cells carrying a non-selectable, targeted gene mutation at a locus of interest, and therefore provides a model which can be used to produce a homozygous mutation of any gene, regardless of its function, if a cloned fragment of the gene is available (see page 348, second paragraph, line 1-3, third paragraph, line 1-5, and page 352, fourth paragraph, line 1-3). Mansour et al. further teach the generation of two targeting constructs, pRV9.1/TK and pINT-2-N/TK, each contains two sequences from an hprt gene and an int-2 gene respectively, and a neo selection marker gene in between the two sequences (see page 350, figure 3). However, Mansour et al. do not teach how to make a magnesium-dependent phosphatase gene targeting construct and knockout mouse.

Medvedev et al. teach that RORγ is induced during fat cell differentiation and expressed abundantly in T lymphocytes but not in B lymphocytes, suggesting a role in regulating both adipocyte function and specific T-cell functions (see page 101, lines 1-8). Medvedev et al. also

teach that genetic alterations involving the human 1q21 region where the RORγ gene is located have been implicated in a variety of malignancies including lymphomas and renal carcinomas. Medvedev et al. suggest that further studies need to be done to determine whether genetic alterations in the RORγ gene are involved in these disease processes (page 101, lines 9-16). Medvedev et al. further teach the cloning of the mouse RORγ gene and provided the genomic sequence of this gene (see Figure 1).

Based on the teaching of Medvedev et al. that RORγ is involved in regulating both specific T cell and adipocyte function, it would have been obvious to one of ordinary skill in the art to knockout the RORγ to study its function. The ordinary artisan would have been motivated to knockout the expression of the RORγ gene because of its possible involvement in the disease process of lymphomas, as suggested by Medvedev et al. The ordinary artisan would have had reasonable expectation of success for making such a knockout targeting construct and subsequently generating a knockout mouse because of the teachings of Mansour et al., who teach a general method of targeted gene disruption in mice based on homologous recombination using a cloned fragment of a desired gene, and Medvedev et al., who teach the coding sequence of the mouse RORγ gene. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

***Double Patenting Warning***

Applicant is advised that should claim 97 be found allowable, claim 124 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing,

despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine Qian, Ph.D.